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The geographical ancestry affects normal hemoglobin values in high-altitude residents

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Abstract

Increasing the hemoglobin (Hb) concentration is a major mechanism adjusting arterial oxygen content to decreased oxygen partial pressure of inspired air at high altitude. Approximately 5% of the world's population living at altitudes higher than 1500 m shows this adaptive mechanism. Notably, there is a wide variation in the extent of increase in Hb concentration among different populations. This short review summarizes available information on Hb concentrations of high-altitude residents living at comparable altitudes (3500-4500 m) in different regions of the world. An increased Hb concentration is found in all high-altitude populations. The highest mean Hb concentration was found in adult male Andean residents and in Han-Chinese living at high altitude, whereas it was lowest in Ethiopians, Tibetans, and Sherpas. A lower plasma volume in Andean high-altitude natives may offer a partial explanation. Indeed, male Andean high-altitude natives have a lower plasma volume than Tibetans and Ethiopians. Moreover, Hb values were lower in adult, non-pregnant females than in males; differences between populations of different ancestry were less pronounced. Various genetic polymorphisms were detected in high altitude residents thought to favor life in a hypoxic environment, some of which correlate with the relatively low Hb concentration in the Tibetans and Ethiopians, whereas differences in angiotensin-converting enzyme allele-distribution may be related to elevated Hb in the Andeans. Taken together these results indicate different sensitivity of oxygen dependent control of erythropoiesis or plasma volume among populations of different geographical ancestry, offering explanations for differences in the Hb concentration at high altitude.

Introduction

At high altitude, tissue oxygen supply is compromised by reduced oxygen loading of hemoglobin (Hb) because of decreased inspiratory and alveolar oxygen partial pressure (PO_2) and impaired alveolar diffusion. Because of the sigmoidal shape of the oxygen dissociation curve (ODC) arterial oxygen saturation (SaO_2) and arterial blood oxygen content decrease in a non-linear fashion with increasing altitude. At altitudes up to approximately 3000 m the flat upper portion of the ODC prevents a decrease in SaO_2 to values below 90%. However, above 3000 m the decrease in SO_2 is more pronounced because of the steep middle portion of the ODC (70). Compensation by hyperventilation, increased oxygen affinity of Hb, and increased cardiac output is incomplete.

In 1891, Viault (114) first reported that the erythrocyte count increased in lowlanders after ascending to Morococha (4540 m). The related increase in the Hb concentration effectively prevents a decrease in arterial oxygen content. Several mechanisms (summarized in figure 1) control the increase in Hb concentration in response to hypoxia: (1) Plasma volume decreases within a few days after lowlanders ascend to high altitude. Ultimately, this process increases hematocrit levels and Hb concentration. (2) Stimulation of erythropoiesis elevates total erythrocyte number and total Hb mass, which takes approximately 7-10 days (89, 101). Stimulated erythropoiesis and Hb synthesis also require sufficient supply of iron, which is obtained from storage compartments (e.g. liver or splenic macrophages) and nutritional intake to prevent hypochromic anemia (37).

It is notable that an increase in total Hb mass will only elevate the Hb concentration in the absence of a proportional increase in plasma volume which is the case at high altitude (90). Thus, an elevated Hb concentration may not necessarily be a sign of stimulated erythropoiesis. The advantage of the elevated Hb concentration at high altitude is an increased amount of oxygen contained in a given stroke volume of the heart that results in an increased amount of oxygen delivered to the periphery. An adverse effect is increased blood viscosity that increases the heart's workload. By contrast, in athletes, training increases the plasma volume more than the total erythrocyte volume resulting in normal or even decreased hematocrit and Hb concentration (51) thereby avoiding increased blood viscosity, that in turn improves microcirculation and thus oxygen supply to working skeletal muscles without reducing perfusion of other organs (98).

In sojourners, the magnitude of increase in Hb concentration and in total Hb-mass varies with altitude and the duration of their stay. It may take weeks to months to reach a new steady-state (35, 89, 101). The increased Hb concentration restores the pre-altitude values of arterial oxygen content within a few weeks of a sojourn at high altitude (21, 101). However, sea level maximal oxygen uptake is not restored because the arterial oxygen partial pressure - which determines the driving force for the diffusion of oxygen from blood capillaries to the cells - is not compensated by increasing the Hb concentration (21).

Whereas several millions of people travel to high altitude and stay there for a relatively short period of time, a little more than 5 % of the world's population lives permanently at altitudes higher than 1500 m (~ 5000 ft) on approximately 4 % of the world's populated land area (27) (48). Life at these altitudes therefore results in unique patterns of adaptation to improve tissue oxygenation despite decreased inspiratory oxygen partial pressure. An elevation of the Hb concentration that correlates with the altitude of residence is part of this adaptive response (e.g. (118)). Adaptation is best documented by the superior exercise performance in the hypoxic environment or enhanced reproductive capacity of native highlanders in comparison with lowlanders who had ascended recently (19, 38). On the other hand, there also seems to be a higher prevalence of anemia in high altitude residents of the Peruvian Andes (44) and in Ethiopians (96), at least when its diagnosis is based on the standards defined by the World Health Organization (WHO) that defines the cut-off at 13 g/dl for adult males and 12 g/dl for adult females at sea-level; values are then adjusted for altitude (1, 79). However, those cut-off values might be too high (44, 96) and might not apply to different ethnicities (36). There is also mal-adaptation in high altitude residents suffering from chronic mountain sickness, which is in part characterized by hypoxemia despite of an aggravated increase in the Hb concentration (65).

In this short review we describe adjustments of the Hb concentration of native highlanders of different ancestry residing in different regions/countries of the world ("geographical ancestry") and discuss possible mechanisms contributing to the different patterns of adaptation of their Hb-concentration. Unfortunately, data on the Hb concentration of high-altitude residents are incomplete in terms of residential altitude, age, sex, pregnancy, and other factors that might affect blood oxygen content and erythropoiesis. Therefore we focus mainly on adult males and non-pregnant females residing at altitudes between 3500 m and 4500 m. Results on the altitudedependency of the Hb concentration, which also indicate the gaps, are summarized in a meta-analysis by Gassmann et al. (36).

Hb concentration in high altitude natives

It is important to note that numerous studies report results on mixed populations without mention of their exact ethnic affiliation. Examples are the Ethiopian populations of the Amharas and the Oromo, or the Andean Aymaras and Quechuas.

Hb in males at high altitude. Hb concentrations in blood vary little among age- and sex matched healthy individuals living near sea level in different countries of the world. The Hb concentration increases with altitude of residence (75). However, there is increasing evidence that the magnitude of elevated Hb concentrations differs among highlanders from different countries around the world thereby indicating possible effects of ancestry on the adaptation to high altitude (6, 36). **Figure 2** (upper panel) summarizes averaged Hb concentrations of males living at altitudes between 3500 and 4500 m. These data were extracted from nearly 100 publications on high-altitude physiology (in its broadest sense) reporting on patterns of adaptation to high altitude. It compares Hb concentrations with values obtained from the corresponding groups residing at low altitude. The upper panel of figure 2 shows that Hb concentrations of adult males vary by up to 2 g/dl between the different high-altitude populations (black symbols). Publications on South American Quechuas reported Hb concentrations approximately 1.5 g/dl lower than in those where the ethnic origin of the Andean study-population had not been specified. It is not clear whether the higher Hb concentration in the latter group can be assigned to Aymaras, the other major indigenous Andean population. Indeed, a difference between Quechuas and Aymaras has been pointed out by Arnaud et al. (5), who found a Hb concentration of 18.2 g/dl in Aymaras but only 15.8 g/dl in Quechuas living at 3600 m. Interestingly, also the Hb concentration of Quechuas living at altitudes < 450 m was lower than that of Aymaras (13.2 vs. 14.8 g/dl, respectively) (5). The interpretation of these results is difficult because the groups analyzed consisted of a mix between men and women (5), although to comparable proportions (64% males and 36% females).

Many studies focused on the Hb concentration of native Tibetan highlanders and compared these values to those of Han Chinese who had moved to the Tibetan plateau within the last decades and who resided there for at least several years. Figure 2 indicates that the average Hb concentration in Tibetan natives was approximately 1.7 g/dl lower than the values reported for high-altitude Han Chinese (33). It is of note that Han-Chinese born and raised in the Tibetan highlands showed improved adaptation compared to their first-generation (116). Similarly, the Hb concentration of Himalayan Sherpas and of Ethiopian highland natives was lower than that of Han-Chinese and non-Quechua South Americans living at comparable altitudes (figure 2).

A gold standard would be to compare Hb values from high-altitude natives with the same ethnical group living at low altitude. Unfortunately, these comparisons are rare and study groups are small. Furthermore, some of the available data were obtained after subjects had moved from high-altitude to near sea-level and resided there for only very short time before analysis. Thus, it is unclear whether measured Hb concentrations resemble a true steady state. Currently, there are no data on Ethiopians living near sea-level; the lowest altitude reported was 1097 m (97). Figure 2 (upper panel; open symbols) indicates that those groups with lower Hb concentration at high altitude (Quechuas, Ethiopians and Tibetans) also appear to show lower Hb values near sea level compared to the non-Quechua South American and the Han Chinese male highlanders. Additional studies are needed to confirm these observations.

From the data shown in figure 2 (upper panel), the magnitude of increase in the Hb concentration per altitude-increment can be estimated. However, this is based only on a low number of available data on respective low altitude residents. Best estimates come from Andean populations (non-specified ancestry and Quechuas), where the increase in Hb concentration with altitude amounts to approximately 3.6 g/dl per 4000 m (0.9 g/1000 m), which compares well with our recent meta-analysis showing an increase of ~1 g/1000 m as calculated by a linear regression model (36). The increase in the Hb concentration with altitude was considerably lower in Han Chinese and in Tibetans and amounted to approximately 2.5 g/dl per 4000 m (≈0.6 g/dl/1000 m), comparing well to the results from a meta-analysis (36). Calculation of increments for Ethiopians and Sherpas cannot be justified because of limited data-availability.

Together these results indicate that Han-Chinese, similar to non-acclimatized lowlanders (56, 114), but also certain South American Andean populations, who had settled in highland regions approximately 12,000 years ago (39), show a higher Hb concentration than populations that likely had entered high-altitude regions of the Tibet 30,000 to 40,000 years ago (126) and up to 70,000 years in Ethiopia (see (102)). Of note, these differences in the Hb concentration between populations of different ancestry appear to persist when these highlanders move to low altitude. Results also indicate that the increment in Hb concentration with altitude varies among populations of different ancestry, which might point to genetic differences in the sensitivity of oxygen dependent systems controlling Hb concentration such as erythropoiesis and plasma volume regulation.

Hb in females at high altitude. Data on adult females and pregnant females are scarce. Frequently, sea-level reference groups are missing, pointing out the need for further studies. **Figure 2** (lower panel) summarizes mean Hb concentrations from adult, non-pregnant women of different geographical ancestry living near sea level or at altitudes between 3500 and 4500 m. Similar to men, the highest mean Hb concentrations are found in South Americans (no ancestry specified), and they appear higher than those of Tibetans and Sherpas. However, in contrast to men there are no striking differences between populations of different ancestry. It is interesting that Hb values from the different studies on South American and on Tibetan women show a wider distribution than the others. It is not known, whether this is associated with the iron status. Although there are only few sea-level data (most complete data are on South American and Han-Chinese women) figure 2 shows a pronounced increase in Hb concentration with altitude. Please note that because of lack of data we chose Kenyans as control group for Ethiopians. In addition, some data on sea-level South Americans are from national surveys from Peru. From the data available an increase in the Hb concentration of approximately 2.5 g/dl per ~3500 m can be estimated for South American women and ~ 2 g/dl per 3500 m in Han Chinese. These results agree well with results from a meta-analysis (36). Comparison of Hb-values of males and females in figure 2 also shows the well-known sex difference in the Hb concentrations of approximately 2 g/dl higher values in adult males than in the non-pregnant females at sea level (see (79)), and indicates that this difference persists in high-altitude residents (36).

Hb in children at high altitude. At low altitude the Hb concentration of children changes significantly with age: the Hb value at birth (up to 20 g/dl) is even higher than in adults (most likely representing a compensation for decreased oxygen partial pressure in the umbilical vein and in the inferior vena cava), followed by a decrease within the first few months of life. Then the Hb concentration increases similarly in girls and boys beginning at approximately 11 g/dl and reaching typical adult values at an age of approximately 15 years in women while in males, Hb values continue to increase up to an age of approximately 20 years (e.g. (32, 55)). This continued increase explains the higher Hb concentration of adult men compared to women (e.g. (32, 55)). The Hb concentration of newborns at altitudes >3000 m varies between approximately 15 -17 g/dl in the USA (81), in Quechuas (34) and in Tibetans (81) but was approximately 19 g/dl in Han-Chinese (81) and Andeans of non-specified ethnicity (38), which is close to the range of newborns at low altitude. Garruto et al. (33) compared Hb concentrations of Tibetan and Han Chinese children, juveniles, and young adults living at different altitudes (3200 – 4300 m) in the Tibet. The authors showed that the age-related increase in Hb values was similar in children living at different altitude ranges and that, similar to sea level but independent of altitude, adult Hb values were reached at approximately the same age at either altitude. In all age-groups, the Hb concentration was higher at the higher altitudes. In some age groups there were lower Hb values in male Han Chinese than in Tibetan; there was almost no difference in females. However, numbers of individuals in each group were small (33). Wu et al. (120) compared Hb concentrations of 5 to 15 year old boys and girls (note that the Hb concentration changes significantly within this age range (32)) of Han-Chinese and of Tibetan ancestry living at different altitudes and found no difference between both sexes, which is consistent with above mentioned literature at low altitude (32). They also showed that the Hb concentrations increase with altitude of residence in both ethnic groups but that the increment was less pronounced in Tibetan than in Han-Chinese children. The review by Weitz et al. (116) showed an increase in Hb with the age of the children. Furthermore, they found comparable Hb values in Han Chinese and Tibetan children living between 3600 m and 4000 m (116). A dataset on more than 2 million Peruvian children of different ages (5 to 59.9 months) living at altitudes from sea level to >4000 m has been analyzed by Orcas-Cordova et al. (82). They showed a mild increase in Hb concentration from 11.0 g/dl (5 to 11.9 months) to 11.8 g/dl (36 to 59.9 months), which occurred independently of the children's residential altitude. Hb concentration of all ages combined increased with altitude from 11.3 at sea level to 13.9 g/dl at >4000 m; this increment with altitude was similar in all age-subgroups (82). Taken together, these results indicate that the increment in Hb concentration with age persists at high altitude and that the magnitude of increase in the children seems comparable to that of adults.

Smokers and smoke-exposed individuals are an interesting subgroup. Carbon monoxide (CO) binds to Hb and reduces oxygen binding because of the higher affinity of CO to Hb (for review see (70)). In fact, a compensatory elevation in the Hb concentration had been noticed at sea level (85). At high altitude CO-Hb-binding theoretically will increase the degree of hypoxia that might also aggravate the increase in Hb concentration. Guleria et al. (50) studied Ladakhi natives living at an altitude of 3658 m; only six out of 25 were non-smokers (number of cigarettes per day not recorded). Unexpectedly their data revealed no difference in the Hb concentration between both groups. In contrast, Brewer et al. (18) reported that a small proportion of male and female residents of Leadville, CO (~ 3100 m), was polycythemic and noticed that almost all of them were smokers. Whereas the Hb concentration of non-smokers living at Leadville was 15.98 ± 1.67 g/dl, those of heavy smokers was elevated by approximately 1.7 g/dl (17). Elevated Hb values were also found in Bolivian high-altitude natives, who smoked relative to their non-smoking counterparts (100). Similarly, elevated CO-Hb caused by indoor air pollution from open fire was also associated with elevated Hb concentration in iron-deficient Mayan women living in rural highland communities of Guatemala (2200 to 2900 m) but, however, not in those with normal ferritin levels (80). In summary, these results point to an elevated Hb concentration in compensation for increased CO-Hb levels independent of the altitude of residence, but systematic analyses are not available.

Limitations of Hb-data. A major limitation of most studies is the low number of subjects analyzed. Much larger numbers and a much wider variety of ancestries needs to be studied to obtain a more complete picture providing a stronger basis for studies on the mechanisms causing elevated Hb concentrations at high altitude and for the definition of cut-off values used to determine anemia and polycythemia. A significant number of studies combined results obtained on men and women despite common knowledge of sex differences in the Hb concentration in adults. Similarly, the age of study subjects was frequently chosen carelessly by including study subjects whose Hb concentration had not yet reached the stable values of adulthood. Differences in the Hb concentration at sea level between populations of different ancestry are not well described. The best-documented difference is the lower Hb concentration (- 1 g/dl) in people of African ancestry in comparison to Caucasians living in the Unites States of America, which seems to be independent of sex and age (30, 32). It is not known, however, which pattern of change in Hb concentration this group follows when exposed to high altitude.

Mechanisms causing elevated Hb concentration in high altitude residents

Figure 1 shows that several mechanisms control the adjustments in the oxygen carrying capacity to high altitude. Those mechanisms are effective in both, lowlanders ascending to high altitude as well as in high-altitude residents.

Iron is a major requirement for heme synthesis in erythroid precursors during their maturation, and iron demand is further increased when erythropoiesis is enhanced at high altitude (54). Reduced iron availability often causes iron-deficiency anemia characterized by low Hb concentration and hypochromic anemia. Major causes of iron-deficiency anemia are insufficient nutritional intake and reabsorption, impaired release from iron stores, and chronic blood loss, situations that need to be considered when attempting to diagnose anemia based on the Hb concentration (see (22) for review). Literature on iron demand and on iron status of high-altitude residents will not be discussed further in this short review.

Plasma volume. Plasma volume decreases rapidly after lowlanders ascend to high altitude (101). It remains low even during a one-year's stay (90). Plasma volume is also decreased in high altitude residents (95), and increases when those descend to sea level (90). As a consequence, the Hb concentration is increased in high-altitude residents (90), which adds to the elevation in Hb by enhanced erythropoiesis (see above). Early studies have been performed on Andean high-altitude natives without further discrimination between Aymara and Quechua. Plasma and blood volumes of Kenyan elite runners, who lived and trained at approximately 2000 m above sea-level, were comparable to volumes measured in German athletes near sea-level (88). However, measurements had been performed after the Kenyans had traveled to Germany, which may have been sufficient to increase plasma volume. Claydon et al. (26) reported a larger plasma volume in Ethiopians residing at an altitude of 3622 m than in Peruvian high-altitude natives (4338 m) which seems to account for the lower hematocrit in the Ethiopians. It is unclear, whether the difference in the residential altitude accounts for this difference. In a recent article, Stembridge et al. (106) confirm the higher Hb values in Andean highlanders (4340 m) than in Sherpas (5050 m) despite the pronounced difference in residential altitude. However, the two populations did not differ in total blood volume, which was higher than the blood volume of lowlanders, who spent 5 to 10 days at 5050 m in the Himalayans. The difference is due to a greatly elevated plasma volume in Sherpas. This result points out the significant role of plasma volume in defining the Hb concentration in high-altitude natives.

The mechanisms causing the decrease in plasma volume during hypoxia and the difference among high altitude populations are not well understood. It has been indicated that a decrease in plasma volume is related to elevated erythropoietin levels because it occurred also in normoxic individuals treated with erythropoietin (68). A decreased activity of the renin-angiotensin-aldosterone system resulting in decreased aldosterone formation (Figure 1) in response to hypoxia also contributes to the decrease in plasma volume upon ascent to high altitude. Decreased aldosterone levels reduce renal sodium-reabsorption and subsequently increase water excretion. Elevated catecholamine levels, which block the release of aldosterone from the adrenal glands, might enhance this effect (73). Indeed, high altitude Andean natives have decreased aldosterone-to-renin ratios (4).

The angiotensin-converting enzyme (ACE) controls aldosterone synthesis and release and, thus, Na-balance and extracellular fluid volume. It also affects arterial blood oxygenation in many ways (119). A meta-analysis of literature on a total of 582 high altitude residents and 487 lowlanders revealed no difference in the frequency of I and D alleles among Andean populations (115). No difference in allele frequencies was found between Andean Quechuas and a lowland native American population from the Canadian West Coast; however, the frequency of the I/I genotype was much higher in these populations than in Caucasians (92). There is literature showing a correlation between elevated Hb concentration of the Andean population with increased frequency of the I/I and I/D genotypes of ACE (57, 92, 93). In Chileans, the I/I-genotype was associated with decreased ACE-activity (57), putatively explaining decreased aldosterone plasma levels. Interestingly, the elevated frequency of the I-allele of ACE was related to increased oxygen saturation in Peruvian Quechua (15). Moreover, elevated levels of atrial natriuretic peptide (ANP) produced in the heart enhance renal Na and water excretion, a mechanism that most probably further contributes to plasma volume loss at high altitude. Hypoxia, via HIF-dependent mechanisms, seems to enhance ANP transcription (25). However, results on ANP concentration in plasma of high-altitude residents are divergent.

These results indicate that variations in the control of fluid balance among groups of different ancestry might cause variations in the decrease in plasma volume in high altitude residents. In turn, these different control mechanisms might account for the differences in the Hb concentration among high altitude residents of different ethnicity. Once again, this aspect has not been studied extensively and systematic studies on differences between ethnic groups are lacking.

Genetic variations in the oxygen-sensing system. A variety of polymorphisms has been associated with high altitude acclimatization, some of which correlate with the Hb concentration in blood. A polymorphism resulting in gain of function of *EGLN1*, the gene encoding for the oxygen sensor prolyl hydroxylase-2 (PHD-2), in combination with a polymorphism in the *EPAS1* gene encoding for the hypoxia-inducible factor HIF-2α has been found in Tibetan highlanders who show low Hb concentration (9, 105, 110). These polymorphisms in genes coding for key proteins involved in oxygen sensing mechanisms were not detected in Andean highlanders (16, 37). Accordingly, it has been postulated that these polymorphisms cause the decrease in the PHD-2/HIF-2/erythropoietin axis thereby possibly explaining the blunted response of erythropoiesis to hypoxia in Tibetans. It might, however, also lead to the decreased Hb values of Tibetans living at low altitude (84). In Ethiopians living at different altitudes several candidate genes have been implicated to play a role in high altitude adaptation, some of which might play a role in controlling the HIF-pathway (97).

Androgens. Androgenic steroids, which are strong stimulators of erythropoiesis (99), were shown to be elevated in South American highlanders with abnormally elevated Hb values who also suffered from chronic mountain sickness (42). A genetic basis has not yet been demonstrated. However, studies on children and adults indicate that the elevated Hb in healthy Peruvians was related to altitude but not to androgen levels (40, 41).

Summary and perspectives

Literature summarized above shows clearly that the mean Hb concentration increases with the altitude of residence and that the magnitude of this increase varies among populations of different ancestry. This is an important finding because a decreased Hb concentration is the first line of evidence to diagnose anemia. Based on the differences in the Hb concentration at a specific altitude of residence a single cut-off-value defining a state of anemia intended for world-wide application as suggested by the WHO many decades ago (see e.g. (1, 79)) appears inappropriate (36, 44, 46, 82, 96). Although there is some evidence that the magnitude of the change of Hb values with altitude is comparable in males and females of different ages, and in pregnancy, additional studies are required to strengthen this argument. It is not well understood how other situations interfering with tissue oxygenation such as exposure to carbon monoxide (smoking, open fire cooking/heating), the nutritional status (supply with vitamins and iron), and heavy metal poisoning (e.g. in mining and chemical industry) affect Hb values at high altitude. Therefore, studies with critical selection of phenotypes with demonstrable effects on reproductive success, the calculation of actual fitness costs, and greater inclusion of women among the subjects are warranted (75) not only to detect anemia but to provide a basis for nutritional and health measures that might improve the hematologic status of anemic high altitude residents (107).

The mechanisms contributing to increased Hb concentrations and differences among populations of different ancestry are incompletely understood because only a few ethnicities have been studied in terms of the relation between Hb concentration, total Hb mass, and plasma volume. Although variations in certain candidate genes indicate differences in the activity of the HIF pathway between populations of different ancestry, it is not clear whether this pathway controls erythropoiesis, plasma volume, or both, to explain the differences in Hb concentrations between high altitude populations of different ancestry. However, although ancestry-dependent differences in the systems controlling the Hb concentration improve our understanding of physiological mechanisms of adaptation to hypoxia, their clinical applicability may be of limited value because of pronounced world-wide migration and mixing of populations of different ancestry.

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References

1. WHO.Haemoglobin concentration for the diagnosis and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World health Organization, 2011 (WHO/NMH/NHD/MNM/11.1) (http://www.who.int/vmnis/indicators/haemoglobin.pdf).
2. Adams WH and Strang LJ. Hemoglobin levels on persons of tibetan ancestry living at high altitude. *Proc Soc Exp Biol Med* 149: 1036-1039, 1975.
3. Alkorta-Aranburu G, Beall CM, Witonsky DB, Gebremedhin A, Pritchard JK, Di Rienzo A. The genetic architecture of adaptations to high altitude in Ethiopia. *PLoS Genet* 8: e1003110, 2012.
4. Antezana AM, Richalet JP, Noriega I, Galarza M, Antezana G. Hormonal changes in normal and polycythemic high-altitude natives. *J Appl Physiol* 79: 795-800, 1995.
5. Arnaud J, Quilici JC and Riviere G. High-altitude haematology: Quechua-Aymara comparisons. *Ann Hum Biol* 8: 573-578, 1981.
6. Beall CM. Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. *IntegrCompBiol* 46 18-24, 2006.
7. Beall CM, Brittenham GM, Macuaga F, Barragan M. Variation in hemoglobin concentration among samples of high-altitude natives in the Andes and the Himalayas. *Am J Hum Biol* 2: 639-651, 1990.
8. Beall CM, Brittenham GM, Strohl KP, Blangero J, Williams-Blangero S, Goldstein MC, Decker MJ, Vargas E, Villena M, Soria R, Alarcon AM, Gonzales C. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Phys Anthropol* 106: 385-400, 1998.
9. Beall CM, Cavalleri GL, Deng L, Elston RC, Gao Y, Knight J, Li C, Li JC, Liang Y, McCormack M, Montgomery HE, Pan H, Robbins PA, Shianna KV, Tam SC, Tsering N, Veeramah KR, Wang W, Wangdui P, Weale ME, Xu Y, Xu Z, Yang L, Zaman MJ, Zeng C, Zhang L, Zhang X, Zhaxi P,

Zheng YT. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. *Proc Natl Acad Sci USA* 107: 11459-11464, 2010.

10. Beall CM, Decker MJ, Brittenham GM, Kushner I, Gebremedhin A, Strohl KP. An Ethiopian pattern of human adaptation to high-altitude hypoxia. *PROC NATL ACAD SCI USA* 99 17215-17218, 2002.
11. Beall CM, Gebremedhin A, Brittenham GM, Decker MJ, Shamebo M. Blood pressure variation among Ethiopians on the Simien Plateau. *Ann Hum Biol* 24: 333-342, 1997.
12. Beard JL, Haas JD, Tufts D, Spielvogel H, Vargas E, Rodriguez C. Iron deficiency anemia and steady-state work performance at high altitude. *J Appl Physiol* 64: 1878-1884, 1988.
13. Berger J, Aguayo VM, San Miguel JL, Lujan C, Tellez W, Traissac P. Definition and prevalence of anemia in Bolivian women of childbearing age living at high altitudes: the effect of iron-folate supplementation. *Nutr Rev* 55: 247-256, 1997.
14. Bhandari S, Zhang X, Cui C, Yangla, Liu L, Ouzhuluobu, Baimakangzhuo, Gonggalanzi, Bai C, Bianba, Peng Y, Zhang H, Xiang K, Shi H, Liu S, Gengdeng, Wu T, Qi X, Su B. Sherpas share genetic variations with Tibetans for high-altitude adaptation. *Mol Genet Genomic Med* 5: 76-84, 2017.
15. Bigham AW, Kiyamu M, Leon-Velarde F, Parra EJ, Rivera-Ch M, Shriver MD, Brutsaert TD. Angiotensin-converting enzyme genotype and arterial oxygen saturation at high altitude in Peruvian Quechua. *High altitude medicine & biology* 9: 167-178, 2008.
16. Bigham AW, Wilson MJ, Julian CG, Kiyamu M, Vargas E, Leon-Velarde F, Rivera-Chira M, Rodriquez C, Browne VA, Parra E, Brutsaert TD, Moore LG, Shriver MD. Andean and Tibetan patterns of adaptation to high altitude. *Am J Hum Biol* 25: 190-197, 2013.
17. Brewer GJ. 2,3-DPG and erythrocyte oxygen affinity. *Annu Rev Med* 25: 29-38, 1974.
18. Brewer GJ, Sing CF, Eaton JW, Weil JV, Brewer LF, Grover RF. Effects on hemoglobin oxygen affinity of smoking in residents of intermediate altitude. *J Lab Clin Med* 84: 191-205, 1974.
19. Brutsaert T. Why Are High Altitude Natives So Strong at High Altitude? Nature vs. Nurture: Genetic Factors vs. Growth and Development. *Adv Exp Med Biol* 903: 101-112, 2016.
20. Buroker NE, Ning XH, Zhou ZN, Li K, Cen WJ, Wu XF, Zhu WZ, Scott CR, Chen SH. AKT3, ANGPTL4, eNOS3, and VEGFA associations with high altitude sickness in Han and Tibetan Chinese at the Qinghai-Tibetan Plateau. *Int J Hematol* 96: 200-213, 2012.
21. Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, Saltin B. Why is VO2 max after altitude acclimatization still reduced despite normalization of arterial O2 content? *Am J Physiol* 284: R304-R316, 2003.
22. Camaschella C. Iron deficiency Anemia. *New Engl J Med* 372: 1832-1843, 2015.
23. Chen Y, Jiang C, Luo Y, Liu F, Gao Y. An EPAS1 haplotype is associated with high altitude polycythemia in male Han Chinese at the Qinghai-Tibetan plateau. *Wilderness & environmental medicine* 25: 392-400, 2014.
24. Cheong HI, Janocha AJ, Monocello LT, Garchar AC, Gebremedhin A, Erzurum SC, Beall CM. Alternative hematological and vascular adaptive responses to high-altitude hypoxia in East African highlanders. *Am J Physiol* 312: L172-L177, 2017.
25. Chun YS, Hyun JY, Kwak YG, Kim IS, Kim CH, Choi E, Kim MS, Park JW. Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. *Biochem J* 370: 149-157, 2003.
26. Claydon VE, Gulli G, Slessarev M, Huppert TJ, Mezgebu YM, Assefa T, Gebru S, Appenzeller O, Hainsworth R. Blood and plasma volumes in Ethiopian high altitude dwellers. *Clin Auton Res* 15: 325, 2005.
27. Cohen JE and Small C. Hypsographic demography: the distribution of human population by altitude. *Proc Natl Acad Sci USA* 95: 14009-14014, 1998.
28. Cosio G and Yataco A. Valores de hemoglobina en relacion con la altura sobre el nivel del mar. *RevSalOccup* 13: 5-17, 1968.
29. Curran LS, Zhuang J, Droma T, Land L, Moore LG. Hypoxic ventilatory responses in Tibetan residents of 4400 m compared with 3658 m. *Respir Physiol* 100: 223-230, 1995.

30. Dallman PR, Barr GD, Allen CM, Shinefield HR. Hemoglobin concentration in white, black, and Oriental children: is there a need for separate criteria in screening for anemia? *Am J Clin Nutr* 31: 377-380, 1978.
31. Erzurum SC, Ghosh S, Janocha AJ, Xu W, Bauer S, Bryan NS, Tejero J, Hemann C, Hille R, Stuehr DJ, Feelisch M, Beall CM. Higher blood flow and circulating NO products offset high-altitude hypoxia among Tibetans. *PROC NATL ACAD SCI USA* 104: 17593-17598, 2007.
32. Fulwood R, Johnson CL, Bryner JD, Gunter EW, McGrath CR. Hematological and nutritional biochemistry data for persons 6 months - 74 years of age: United States, 1976 - 80. *DHHS Publication No (PHS) 83-1682* 1-183, 1982.
33. Garruto RM, Chin CT, Weitz CA, Liu JC, Liu RL, He X. Hematological differences during growth among Tibetans and Han Chinese born and raised at high altitude in Qinghai, China. *Am J Phys Anthropol* 122: 171-183, 2003.
34. Garruto RM and Dutt JS. Lack of prominent compensatory polycythemia in traditional native Andeans living at 4,200 meters. *Am J Phys Anthropol* 61: 355-366, 1983.
35. Garvican-Lewis LA, Sharpe K and Gore CJ. Time for a new metric for hypoxic dose? *J Appl Physiol* 121: 352-355, 2016.
36. Gassmann M, Mairbaurl H, Livshits L, Seide S, Hackbusch M, Malczyk M, Kraut S, Gassmann NN, Weissmann N, Muckenthaler MU. The increase in hemoglobin concentration with altitude varies among human populations. *Ann N Y Acad Sci* 2019.
37. Gassmann M and Muckenthaler MU. Adaptation of iron requirement to hypoxic conditions at high altitude. *J Appl Physiol* 119: 1432-1440, 2015.
38. Gassmann NN, van Elteren HA, Goos TG, Morales CR, Rivera-Ch M, Martin DS, Cabala Peralta P, Passano Del Carpio A, Aranibar Machaca S, Huicho L, Reiss IK, Gassmann M, de Jonge RC. Pregnancy at high altitude in the Andes leads to increased total vessel density in healthy newborns. *J Appl Physiol* 121: 709-715, 2016.
39. Gomez-Carballa A, Pardo-Seco J, Brandini S, Achilli A, Perego UA, Coble MD, Diegoli TM, Alvarez-Iglesias V, Martinon-Torres F, Olivieri A, Torroni A, Salas A. The peopling of South America and the trans-Andean gene flow of the first settlers. *Genome Res* 28: 767-779, 2018.
40. Gonez C, Donayre M, Villena A, Gonzales GF. Hematocrit levels in children at sea level and at high altitude: effect of adrenal androgens. *Hum Biol* 65: 49-57, 1993.
41. Gonzales GF. [Hemoglobin and testosterone: importance on high altitude acclimatization and adaptation]. *Rev Peru Med Exp Salud Publica* 28: 92-100, 2011.
42. Gonzales GF, Gasco M, Tapia V, Gonzales-Castaneda C. High serum testosterone levels are associated with excessive erythrocytosis of chronic mountain sickness in men. *Am J Physiol Endocrinol Metab* 296: E1319-1325, 2009.
43. Gonzales GF, Lozano-Hernandez R, Gasco M, Gonzales-Castaneda C, Tapia V. Resistance of sperm motility to serum testosterone in men with excessive erythrocytosis at high altitude. *Horm Metab Res* 44: 987-992, 2012.
44. Gonzales GF, Rubin de Celis V, Begazo J, Del Rosario Hinojosa M, Yucra S, Zevallos-Concha A, Tapia V. Correcting the cut-off point of hemoglobin at high altitude favors misclassification of anemia, erythrocytosis and excessive erythrocytosis. *Am J Hematol* 93: E12-E16, 2018.
45. Gonzales GF, Rubio J and Gasco M. Chronic mountain sickness score was related with health status score but not with hemoglobin levels at high altitudes. *Respiratory physiology & neurobiology* 188: 152-160, 2013.
46. Gonzales GF, Tapia V and Gasco M. Correcting haemoglobin cut-offs to define anaemia in high-altitude pregnant women in Peru reduces adverse perinatal outcomes. *Arch Gynecol Obstet* 290: 65-74, 2014.
47. Gonzales GF, Tapia V, Gasco M, Gonzales-Castaneda C. Aromatase activity after a short-course of letrozole administration in adult men at sea level and at high altitude (with or without excessive erythrocytosis). *Horm Metab Res* 44: 140-145, 2012.
48. Gore CJ, McSharry PE, Hewitt AJ, Saunders PU. Preparation for football competition at moderate to high altitude. *Scand J Med Sci Sports* 18 Suppl 1: 85-95, 2008.

49. Guan W, Li X, Yang YZ, Wang J, Feng XY, Xu JH. [Serum levels and significance of HIF-1alpha and HIF-2alpha in healthy Tibetan and Han residents at different altitudes]. *Zhonghua Yi Xue Za Zhi* 93: 3057-3059, 2013.
50. Guleria JS, Pande JN, Sethi PK, Roy SB. Pulmonary diffusing capacity at high altitude. *J Appl Physiol* 31: 536-543, 1971.
51. Heinicke K, Wolfarth B, Winchenbach P, Biermann B, Schmid A, Huber G, Friedmann B, Schmidt W. Blood volume and hemoglobin mass in elite athletes of different disciplines. *Int J Sports Med* 22: 504-512, 2001.
52. Hoit BD, Dalton ND, Erzurum SC, Laskowski D, Strohl KP, Beall CM. Nitric oxide and cardiopulmonary hemodynamics in Tibetan highlanders. *J Appl Physiol* 99: 1796-1801, 2005.
53. Huang SY, Sun S, Droma T, Zhuang J, Tao JX, McCullough RG, McCullough RE, Micco AJ, Reeves JT, Moore LG. Internal carotid arterial flow velocity during exercise in Tibetan and Han residents of Lhasa (3,658 m). *J Appl Physiol* 73: 2638-2642, 1992.
54. Huff RL, Lawrence JH, Siri WE, Wasserman LR, Hennessy TG. Effects of changes in altitude on hematopoietic activity. *Medicine (Baltimore)* 30: 197-217, 1951.
55. Humpeler E, Vogel S, Schobersberger W, Mairbäurl H. Red cell oxygen transport in man in relation to gender and age. *Mechanisms of Aging and Development* 47: 229-239, 1989.
56. Hurtado A, Merino C and Delgado E. Influence of anoxaemia on the hematopoietic acitvity. *Arch Intern Med* 75: 284-323, 1945.
57. Jalil JE, Piddo AM, Cordova S, Chamorro G, Braun S, Jalil R, Vega J, Jadue PL, Lavandero S, Lastra P. Prevalence of the angiotensin I converting enzyme insertion/deletion polymorphism, plasma angiotensin converting enzyme activity, and left ventricular mass in a normotensive Chilean population. *Am J Hypertens* 12: 697-704, 1999.
58. Jeong C, Alkorta-Aranburu G, Basnyat B, Neupane M, Witonsky DB, Pritchard JK, Beall CM, Di Rienzo A. Admixture facilitates genetic adaptations to high altitude in Tibet. *Nat Commun* 5: 3281, 2014.
59. Jiang C, Chen J, Liu F, Luo Y, Xu G, Shen HY, Gao Y, Gao W. Chronic mountain sickness in Chinese Han males who migrated to the Qinghai-Tibetan plateau: application and evaluation of diagnostic criteria for chronic mountain sickness. *BMC Public Health* 14: 701, 2014.
60. Jones RL, Man SF, Matheson GO, Parkhouse WS, Allen PS, McKenzie DC, Hochachka PW. Overall and regional lung function in Andean natives after descent to low altitude. *Respir Physiol* 87: 11-24, 1992.
61. Julian CG, Hageman JL, Wilson MJ, Vargas E, Moore LG. Lowland origin women raised at high altitude are not protected against lower uteroplacental O2 delivery during pregnancy or reduced birth weight. *Am J Hum Biol* 23: 509-516, 2011.
62. Julian CG, Vargas E, Gonzales M, Davila RD, Ladenburger A, Reardon L, Schoo C, Powers RW, Lee-Chiong T, Moore LG. Sleep-disordered breathing and oxidative stress in preclinical chronic mountain sickness (excessive erythrocytosis). *Respiratory physiology & neurobiology* 186: 188-196, 2013.
63. Leon-Velarde F, Arregui A, Vargas M, Huicho L, Acosta R. Chronic mountain sickness and chronic lower respiratory tract disorders. *Chest* 106: 151-155, 1994.
64. Leon-Velarde F, Gamboa A, Chuquiza JA, Esteba WA, Rivera-Chira M, Monge CC. Hematological parameters in high altitude residents living at 4,355, 4,660, and 5,500 meters above sea level. *High altitude medicine & biology* 1: 97-104, 2000.
65. Leon-Velarde F, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L, Ge RL, Hackett P, Kobayashi T, Moore LG, Penaloza D, Richalet JP, Roach R, Wu T, Vargas E, Zubieta-Castillo G, Zubieta-Calleja G. Consensus statement on chronic and subacute high altitude diseases. *High altitude medicine & biology* 6: 147-157, 2005.
66. Leon-Velarde F, Rivera-Chira M, Tapia R, Huicho L, Monge CC. Relationship of ovarian hormones to hypoxemia in women residents of 4,300 m. *Am J Physiol* 280: R488-493, 2001.
67. Levy SB. Hemoglobin differences among Kenyan tribes. A survey of eight tribes in seventeen areas of the country. *Am J Trop Med Hyg* 18: 138-146, 1969.

68. Lundby C, Thomsen JJ, Boushel R, Koskolou M, Warberg J, Calbet JA, Robach P. Erythropoietin treatment elevates haemoglobin concentration by increasing red cell volume and depressing plasma volume. *J Physiol* 578: 309-314, 2007.
69. Lundgrin EL, Janocha AJ, Koch CD, Gebremedhin A, Di Rienzo A, Alkorta-Aranburu G, Brittenham GM, Erzurum SC, Beall CM. Plasma hepcidin of Ethiopian highlanders with steady-state hypoxia. *Blood* 122: 1989-1991, 2013.
70. Mairbäurl H and Weber RE. Oxygen Transport by Hemoglobin. *Compr Physiol* 2: 1463-1489, 2012.
71. McAuliffe F, Kametas N, Krampl E, Ernsting J, Nicolaides K. Blood gases in pregnancy at sea level and at high altitude. *BJOG* 108: 980-985, 2001.
72. Mejia OM, Prchal JT, Leon-Velarde F, Hurtado A, Stockton DW. Genetic association analysis of chronic mountain sickness in an Andean high-altitude population. *Haematologica* 90: 13-19, 2005.
73. Milledge JS. Renin-Aldosterone System. In: *High Altitude and Man*, edited by West JB and Lahiri S. Bethesda: Williams & Wilkins, 1984, p. 47-57.
74. Moore LG. Maternal O2 transport and fetal growth in Colorado, Peru, and Tibet high-altitude residents. *Am J Hum Biol* 2: 627-637, 1990.
75. Moore LG. Measuring high-altitude adaptation. *J Appl Physiol* 123: 1371-1385, 2017.
76. Moore LG, Brodeur P, Chumbe O, D'Brot J, Hofmeister S, Monge C. Maternal hypoxic ventilatory response, ventilation, and infant birth weight at 4,300 m. *J Appl Physiol* 60: 1401-1406, 1986.
77. Moore LG, Zamudio S, Zhuang J, Droma T, Shohet RV. Analysis of the myoglobin gene in Tibetans living at high altitude. *High altitude medicine & biology* 3: 39-47, 2002.
78. Moore LG, Zamudio S, Zhuang JG, Sun SF, Droma T. Oxygen transport in Tibetan women during pregnancy at 3,658 m. *Am J Phys Anthropol* 114: 42-53, 2001.
79. Nestel P. Adjusting hemoglobin values for program surveys. *Internatioanl Nutritional Anemia Consultative Group (INACG)* 2002.
80. Neufeld LM, Haas JD, Ruel MT, Grajeda R, Naeher LP. Smoky indoor cooking fires are associated with elevated hemoglobin concentration in iron-deficient women. *Rev Panam Salud Publica* 15: 110-118, 2004.
81. Niermeyer S, Yang P, Shanmina, Drolkar, Zhuang J, Moore LG. Arterial oxygen saturation in Tibetan and Han infants born in Lhasa, Tibet. *N Engl J Med* 333: 1248-1252, 1995.
82. Ocas-Cordova S, Tapia V and Gonzales GF. Hemoglobin Concentration in Children at Different Altitudes in Peru: Proposal for [Hb] Correction for Altitude to Diagnose Anemia and Polycythemia. *High altitude medicine & biology* 19: 398-403, 2018.
83. Organization TWH. Global Database on Anaemia (WHO). The database on Anaemia includes data by country on prevalence of anaemia and mean haemoglobin concentration. *https://wwwwhoint/vmnis/database/anaemia/countries/en/*.
84. Petousi N, Croft QP, Cavalleri GL, Cheng HY, Formenti F, Ishida K, Lunn D, McCormack M, Shianna KV, Talbot NP, Ratcliffe PJ, Robbins PA. Tibetans living at sea level have a hyporesponsive hypoxia-inducible factor system and blunted physiological responses to hypoxia. *J Appl Physiol* 116: 893-904, 2014.
85. Pincherle G and Shanks J. Haemoglobin values in business executives. *Br J Prev Soc Med* 21: 40-42, 1967.
86. Postigo L, Heredia G, Illsley NP, Torricos T, Dolan C, Echalar L, Tellez W, Maldonado I, Brimacombe M, Balanza E, Vargas E, Zamudio S. Where the O2 goes to: preservation of human fetal oxygen delivery and consumption at high altitude. *J Physiol* 587: 693-708, 2009.
87. Pratali L, Allemann Y, Rimoldi SF, Faita F, Hutter D, Rexhaj E, Brenner R, Bailey DM, Sartori C, Salmon CS, Villena M, Scherrer U, Picano E, Sicari R. RV contractility and exercise-induced pulmonary hypertension in chronic mountain sickness: a stress echocardiographic and tissue Doppler imaging study. *JACC Cardiovasc Imaging* 6: 1287-1297, 2013.
88. Prommer N, Thoma S, Quecke L, Gutekunst T, Volzke C, Wachsmuth N, Niess AM, Schmidt W. Total hemoglobin mass and blood volume of elite Kenyan runners. *Med Sci Sports Exerc* 42: 791-797, 2010.

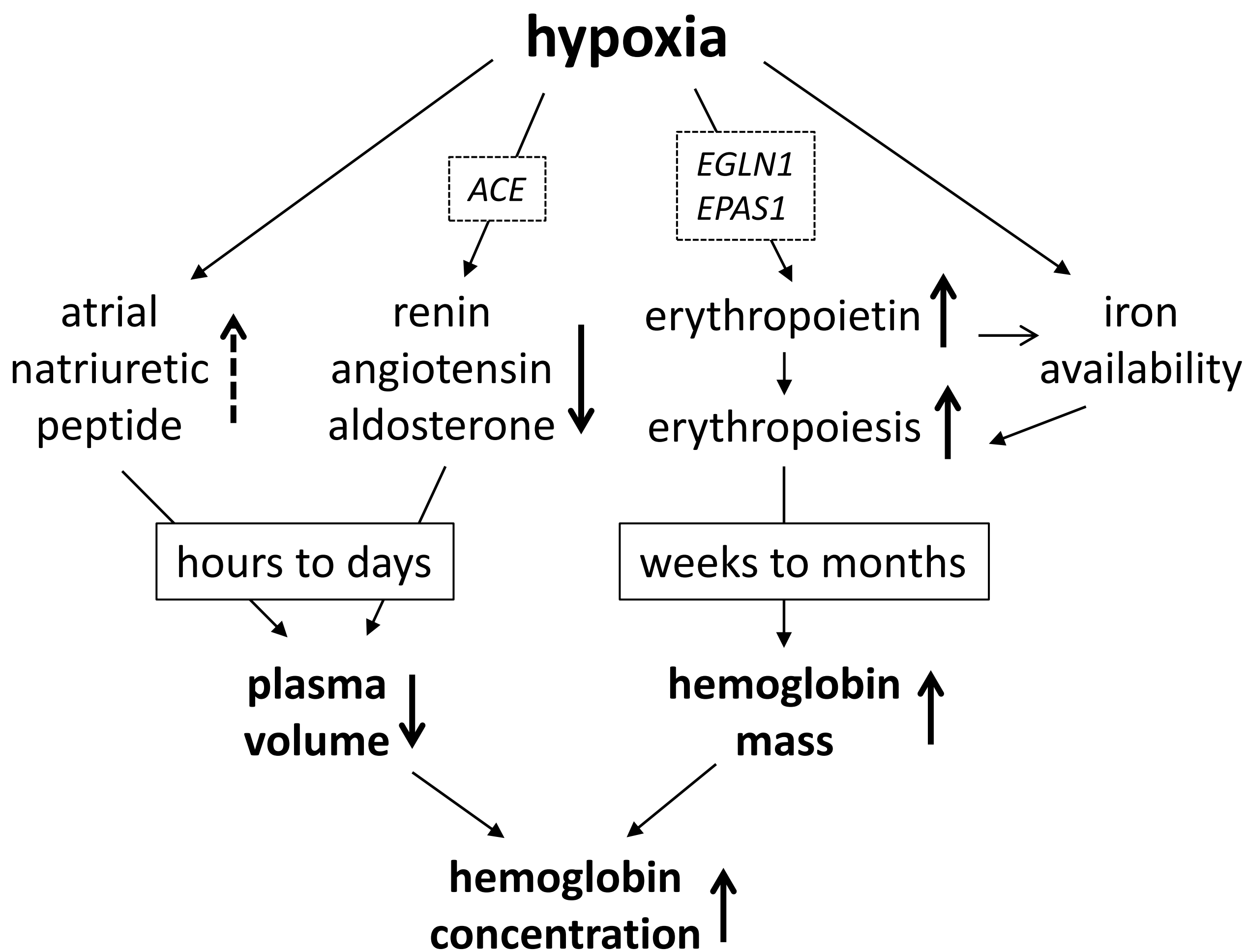
89. Rasmussen P, Siebenmann C, Diaz V, Lundby C. Red cell volume expansion at altitude: a meta-analysis and Monte Carlo simulation. *Med Sci Sports Exerc* 45: 1767-1772, 2013.
90. Reynafarje C, Lozano R and Valdivieso J. The polycythemia of high altitudes: iron metabolism and related aspects. *Blood* 14: 433-455, 1959.
91. Ruiz-Arguelles GJ, Sanchez-Medal L, Loria A, Piedras J, Cordova MS. Red cell indices in normal adults residing at altitude from sea level to 2670 meters. *Am J Hematol* 8: 265-271, 1980.
92. Rupert JL, Devine DV, Monsalve MV, Hochachka PW. Angiotensin-converting enzyme (ACE) alleles in the Quechua, a high altitude South American native population. *Ann Hum Biol* 26: 375-380, 1999.
93. Rupert JL, Kidd KK, Norman LE, Monsalve MV, Hochachka PW, Devine DV. Genetic polymorphisms in the Renin-Angiotensin system in high-altitude and low-altitude Native American populations. *Ann Hum Genet* 67: 17-25, 2003.
94. Samaja M, Veicsteinas A and Cerretelli P. Oxygen affinity of blood in altitude sherpas. *J Appl Physiol* 47: 337-341, 1979.
95. Sanchez C, Merino C and Figallo M. Simultaneous measurement of plasma volume and cell mass in polycythemia of high altitude. *J Appl Physiol* 28: 775-778, 1970.
96. Sarna K, Gebremedin A, Brittenham GM, Beall CM. WHO hemoglobin thresholds for altitude increase the prevalence of anemia among Ethiopian highlanders. *Am J Hematol* 93: E229-E231, 2018.
97. Scheinfeldt LB, Soi S, Thompson S, Ranciaro A, Woldemeskel D, Beggs W, Lambert C, Jarvis JP, Abate D, Belay G, Tishkoff SA. Genetic adaptation to high altitude in the Ethiopian highlands. *Genome Biol* 13: R1, 2012.
98. Schuler B, Arras M, Keller S, Rettich A, Lundby C, Vogel J, Gassmann M. Optimal hematocrit for maximal exercise performance in acute and chronic erythropoietin-treated mice. *Proc Natl Acad Sci U S A* 107: 419-423, 2010.
99. Shahidi NT. Androgens and erythropoiesis. *New Engl J Med* 289: 72-80, 1973.
100. Sharma AJ, Addo OY, Mei Z, Suchdev PS. Reexamination of hemoglobin adjustments to define anemia: altitude and smoking. *Ann N Y Acad Sci* 2019.
101. Siebenmann C, Robach P and Lundby C. Regulation of blood volume in lowlanders exposed to high altitude. *J Appl Physiol* 957-966, 2017.
102. Simonson TS. Altitude Adaptation: A Glimpse Through Various Lenses. *High altitude medicine & biology* 16: 125-137, 2015.
103. Simonson TS, Huff CD, Witherspoon DJ, Prchal JT, Jorde LB. Adaptive genetic changes related to haemoglobin concentration in native high-altitude Tibetans. *Experimental physiology* 100: 1263-1268, 2015.
104. Simonson TS, Wei G, Wagner HE, Wuren T, Bui A, Fine JM, Qin G, Beltrami FG, Yan M, Wagner PD, Ge RL. Increased blood-oxygen binding affinity in Tibetan and Han Chinese residents at 4200 m. *Experimental physiology* 99: 1624-1635, 2014.
105. Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, Prchal JT, Ge R. Genetic Evidence for High-Altitude Adaptation in Tibet. *Science* 329: 72-75, 2010.
106. Stembridge M, Williams AM, Gasho C, Dawkins TG, Drane A, Villafuerte FC, Levine BD, Shave R, Ainslie PN. The overlooked significance of plasma volume for successful adaptation to high altitude in Sherpa and Andean natives. *Proc Natl Acad Sci U S A* 116: 16177-16179, 2019.
107. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, Pena-Rosas JP, Bhutta ZA, Ezzati M, Nutrition Impact Model Study G. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health* 1: e16-25, 2013.
108. Sun S, Oliver-Pickett C, Ping Y, Micco AJ, Droma T, Zamudio S, Zhuang J, Huang SY, McCullough RG, Cymerman A, Moore LG. Breathing and brain blood flow during sleep in patients with chronic mountain sickness. *J Appl Physiol* 81: 611-618, 1996.

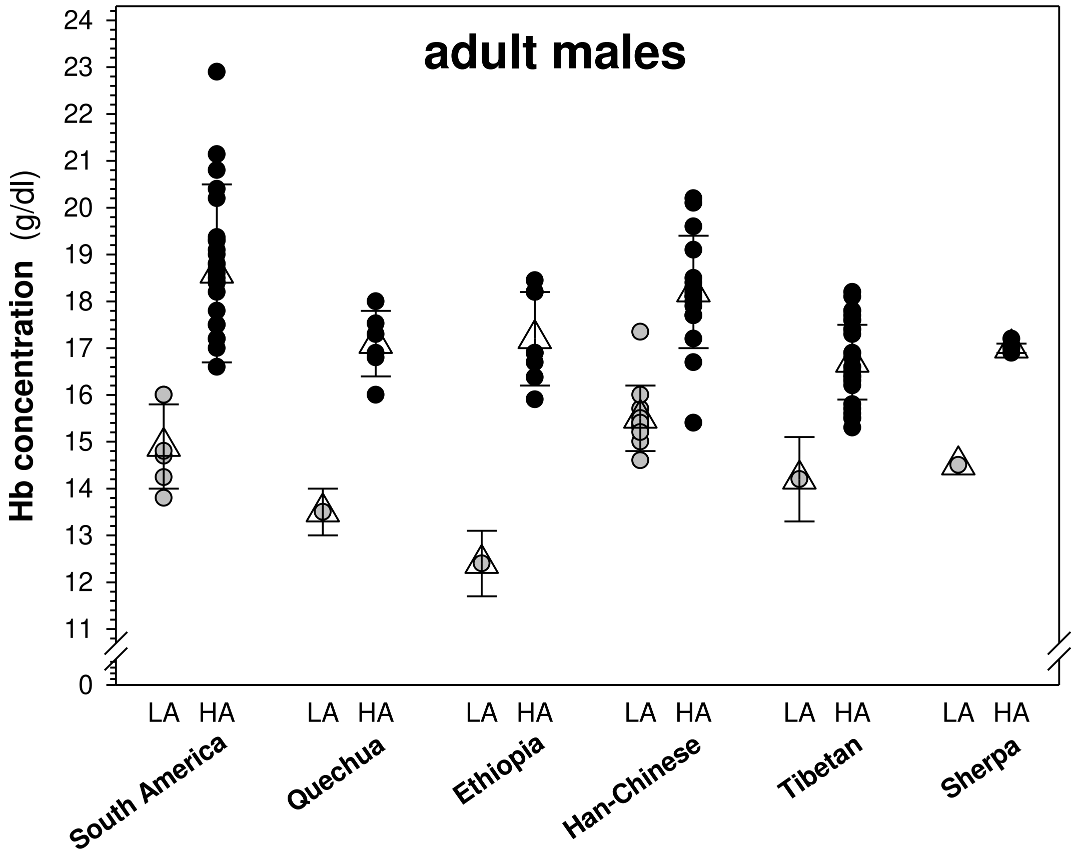
109. Tarazona-Santos E, Lavine M, Pastor S, Fiori G, Pettener D. Hematological and pulmonary responses to high altitude in Quechuas: a multivariate approach. *Am J Phys Anthropol* 111: 165-176, 2000.
110. Tashi T, Reading NS, Wuren T, Zhang X, Moore LG, Hu H, Shestakova A, Lorenzo FR, Burjanivova T, Koul P, Guchhai P, Wittwer CT, Julian CG, Shah B, Huff CD, Gordeuk VR, Prchal JT, Ge RL. Gain-of-function EGLN1 prolyl hydroxylase (PHD2 D4E: C127S) in combination with EPAS1(HIF-2a) polymorphism lowers hemoglobin concentration in Tibetan highlanders. *J Mol Med* 95: 665-670, 2017.
111. Tufts DA, Haas JD, Beard JL, Spielvogel H. Distribution of hemoglobin and functional consequences of anemia in adult males at high altitude. *Am J Clin Nutr* 42: 1-11, 1985.
112. Vargas M, Vargas E, Julian CG, Armaza JF, Rodriguez A, Tellez W, Niermeyer S, Wilson M, Parra E, Shriver M, Moore LG. Determinants of blood oxygenation during pregnancy in Andean and European residents of high altitude. *Am J Physiol* 293: R1303-1312, 2007.
113. Vasquez R and Villena M. Normal hematological values for healthy persons living at 4000 meters in Bolivia. *High altitude medicine & biology* 2: 361-367, 2001.
114. Viault F. Sur la quantite d'oxygene contenue dans la sang des animoux des hauts plateaux de l'Amerique du Sud. *CRH Acad Sci Paris* 112: 295, 1891.
115. Wang Y, Lu H, Chen Y, Luo Y. The association of angiotensin-converting enzyme gene insertion/deletion polymorphisms with adaptation to high altitude: A meta-analysis. *J Renin Angiotensin Aldosterone Syst* 17: 1470320315627410, 2016.
116. Weitz CA, Liu JC, He X, Chin CT, Garruto RM. Responses of Han migrants compared to Tibetans at high altitude. *Am J Hum Biol* 25: 169-178, 2013.
117. Winslow RM, Chapman KW, Gibson CC, Samaja M, Monge CC, Goldwasser E, Sherpa M, Blume FD, Santolaya R. Different hematologic responses to hypoxia in Sherpas and Quechua Indians. *J Appl Physiol* 66/4: 1561-1569, 1989.
118. Winslow RM and Monge C. *Hypoxia, polycythemia, and chronic mountain sickness*. Baltimore: Johns Hopkins Univ.Press, 1987.
119. Woods DR and Montgomery HE. Angiotensin-converting enzyme and genetics at high altitude. *High altitude medicine & biology* 2: 201-210, 2001.
120. Wu T, Wang X, Wei C, Cheng H, Wang X, Li Y, Ge D, Zhao H, Young P, Li G, Wang Z. Hemoglobin levels in Qinghai-Tibet: different effects of gender for Tibetans vs. Han. *J Appl Physiol* 98: 598-604, 2005.
121. Wu TY, Liu FY, Hu L, Wei CY, Wang ZG, Ouzhou L, Cu CY, Bianba, Qi XB, Su B. Hematological parameters in high altitude residents: Tibetan natives versus Han migrants. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* 30: 516-525, 2014.
122. Wu X, Zhao M, Pan B, Zhang J, Peng M, Wang L, Hao X, Huang X, Mu R, Guo W, Qiao R, Chen W, Jiang H, Ma Y, Shang H. Complete blood count reference intervals for healthy Han Chinese adults. *PloS one* 10: e0119669, 2015.
123. Xu J, Yang YZ, Tang F, Ga Q, Wuren T, Wang Z, Ma L, Rondina MT, Ge RL. CYP17A1 and CYP2E1 variants associated with high altitude polycythemia in Tibetans at the Qinghai-Tibetan Plateau. *Gene* 566: 257-263, 2015.
124. Yan Y, Shi Y, Wang C, Guo P, Wang J, Zhang CY, Zhang C. Influence of a high-altitude hypoxic environment on human plasma microRNA profiles. *Sci Rep* 5: 15156, 2015.
125. Yan Y, Wang C, Zhou W, Shi Y, Guo P, Liu Y, Wang J, Zhang CY, Zhang C. Elevation of Circulating miR-210-3p in High-Altitude Hypoxic Environment. *Front Physiol* 7: 84, 2016.
126. Zhang XL, Ha BB, Wang SJ, Chen ZJ, Ge JY, Long H, He W, Da W, Nian XM, Yi MJ, Zhou XY, Zhang PQ, Jin YS, Bar-Yosef O, Olsen JW, Gao X. The earliest human occupation of the high-altitude Tibetan Plateau 40 thousand to 30 thousand years ago. *Science* 362: 1049-1051, 2018.
127. Zhong R, Liu H, Wang H, Li X, He Z, Gangla M, Zhang J, Han D, Liu J. Adaption to High Altitude: An Evaluation of the Storage Quality of Suspended Red Blood Cells Prepared from the Whole Blood of Tibetan Plateau Migrants. *PloS one* 10: e0144201, 2015.

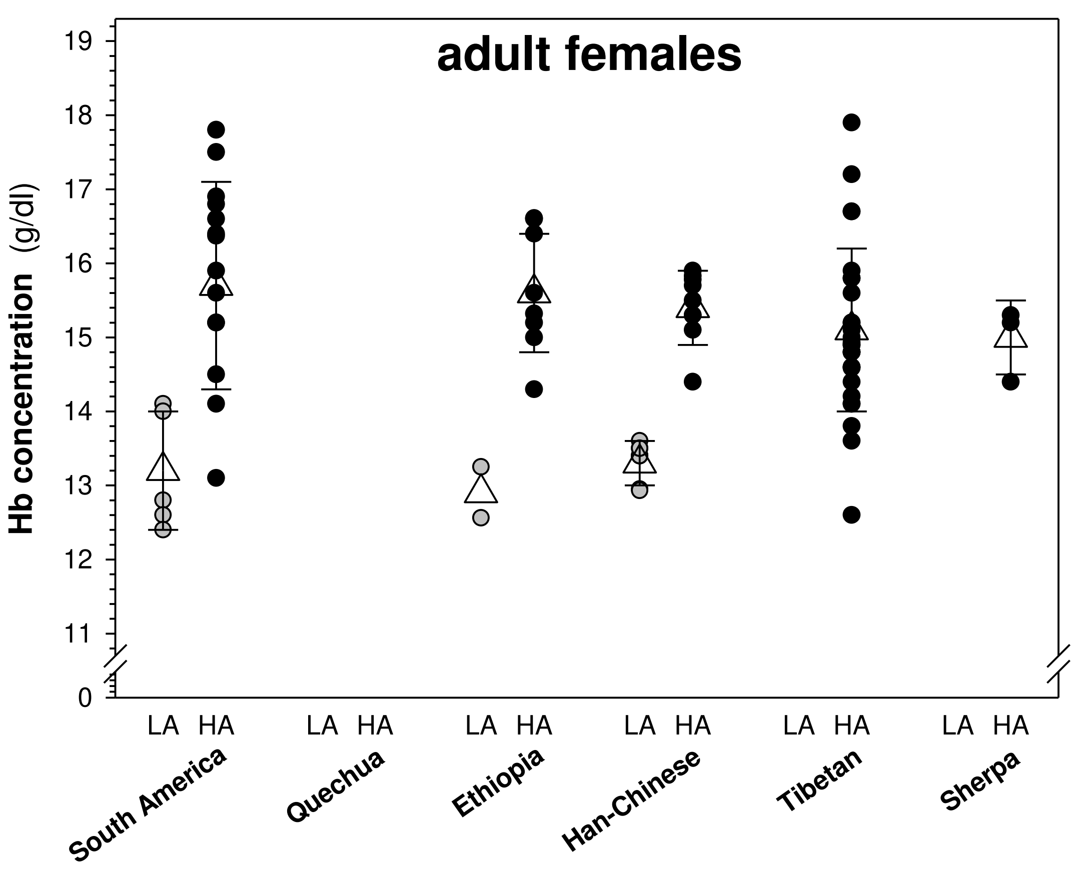
Figure Legends

Figure 1. Mechanisms increasing the hemoglobin concentration at high altitude. *Hypoxia initiates a variety of mechanisms that ultimately all cause an increase in the Hb concentration and thus elevate the oxygen content of arterial blood. Hypoxia stimulates the release of the atrial natriuretic peptide (ANP) from the heart (25) and decreases formation and release of aldosterone via the renin-angiotensin axis (4). Both together impair Na-retention, decrease plasma volume, and thus increase hematocrit and Hb concentration (101). This mechanism might be enhanced by an increased frequency of the I/I-allele of angiotensin converting enzyme (ACE) as found in Andean highlanders (57). Oxygen sensing by prolyl hydroxylases (PHDs) rapidly stabilizes hypoxia inducible factors and in turn raises mRNA levels of erythropoietin within hours upon exposure to hypoxia. However, it takes weeks to months of exposure to high altitude to reach a significant increase in the total number of erythrocytes in blood. A genetic polymorphism increases PHD-2 activity, which, together with a polymorphism of the EGLN1-gene encoding for HIF-2*α*, seems to blunt the erythropoietic response in Tibetans (103). Effective stimulation of erythropoiesis also requires adequate nutritional iron intake, sufficiently filled iron stores, and tight control of intestinal reabsorption and release from stores (37).*

Figure 2. Comparison of Hb concentration of Andean, Ethiopian, Han Chinese, Tibetan, and Sherpa indigenous adult male and female low- and highlanders *(age 18 – 59 years) residing at altitudes between 3500 and 4500 m. (HA, high altitude; black symbols) and respective low altitude controls (LA; grey symbols). Triangles/error bars show the mean values ± SD of the respective set of data. Mean Hb concentrations is reported in the following references.* ***Males, low altitude (LA)****: South America (ancestry not specified; 77 ± 80 m; (28, 42, 43, 47, 56, 91)); Quechua (37 days after descent to sea level; (60)); Ethiopia (1097 m; (97)); Han-Chinese (187 ± 159 m; (49, 84, 122, 124, 125, 127)); Tibet (at least 4 years at sea level; (84)); Sherpas (3 years at 1450 m; n=3 (no SD provided); (94)).* ***Males, High altitude (HA)****: South America (ancestry not specified; 4065 ± 288 m: (7, 8, 12, 28, 42, 45, 47, 56, 62-64, 72, 87, 111, 113)); Quechua (4030 ± 263 m: (94) (34, 109, 117)); Ethiopia (3804 ± 203 m: (3, 10, 24, 69)); Han Chinese (3950 ± 328 m: (20, 23, 33, 49, 53, 59, 104, 108, 120, 124, 125, 127)), Tibetan (4028 ± 313 m: (2, 8, 20, 29, 31, 33, 49, 52, 53, 77, 104, 105, 108, 120, 121, 123-125)); Sherpa (3813 ± 131 m: (2, 58, 94, 117)).* ***Females, low altitude (LA)****: South America (60 ± 25 m; ancestry not specified: (91) (Mexico), (71, 83) (Peru)); Kenya (200 m; (67)); Han-Chinese (187 ± 159 m; (122, 124, 125));* ***Females, high altitude (HA)****: South America (3667 ± 1049 m; ancestry not specified: (7, 8, 13, 16, 45, 61, 64, 66, 76, 86, 112, 113)); Ethiopia (3770 ± 203 m; (3, 11, 24, 69)); Han-Chinese (3718 ± 109 m; (20, 33, 78, 120, 124, 125)); Tibet (3988 ± 330; (8, 20, 31, 33, 52, 74, 77, 78, 105, 120, 123-125)); Sherpas (3600 ± 529; (2, 14, 58)).*


hypoxia
ACE
EGLN1
EPAS1
atrial
natriuretic
peptide
renin
angiotensin
aldosterone
erythropoietin
erythropoiesis
iron
availability
hours to days
weeks to months
plasma
volume
hemoglobin
mass
hemoglobin
concentration


adult males
Hb concentration (g/dl)
24
23
22
21
20
19
18
17
16
15
14
13
12
11
0
LA HA
LA HA
LA HA
LA HA
LA HA
LA HA
South America
Quechua
Ethiopia
Han-Chinese
Tibetan
Sherpa


adult females
Hb concentration (g/dl)
19
18
17
16
15
14
13
12
11
0
LA HA
LA HA
LA HA
LA HA
LA HA
LA HA
South America
Quechua
Ethiopia
Han-Chinese
Tibetan
Sherpa